Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors

M. Moore1*, H. W. Hirte2, L. Siu1, A. Oza1, S. J. Hotte2, O. Petrenciuc3, F. Cihon4, C. Lathia4 & B. Schwartz4

1Princess Margaret Hospital, Toronto, Ontario; 2Juravinski Cancer Centre, Hamilton, Ontario; 3Bayer Inc., Toronto, Canada; 4Bayer Pharmaceuticals Corporation, West Haven, CT, USA

Background: BAY 43-9006, an oral multi-kinase inhibitor, targets serine-threonine kinases and receptor tyrosine kinases, and affects the tumor and vasculature in preclinical models. Based on its pharmacologic effect, it may be a useful cancer treatment. This study determined the maximum tolerated dose (MTD) of BAY 43-9006 in 42 patients with advanced, refractory metastatic or recurrent solid tumors. Dose-limiting toxicities (DLTs), safety, pharmacokinetics and tumor response were also evaluated.

Patients and methods: In this open-label, phase I, dose-escalation study, BAY 43-9006 was administered orally in repeated cycles of 35 days (28 days on/7 days off). Eight doses were investigated: from 50 mg every fourth day to 600 mg twice daily. Treatment continued until unacceptable toxicity, tumor progression or death.

Results: The MTD was 400 mg twice daily. BAY 43-9006 was well tolerated, with mild to moderate toxicities; only six patients discontinued study therapy due to adverse events. DLTs consisted of hand–foot skin reaction in three of seven patients receiving 600 mg twice daily. Stable disease was achieved in 22% of patients; median duration of stable disease was 7.2 months. Consistent with its observed half-life of ~24 h, BAY 43-9006 accumulated on multiple dosing. Increases in exposure were less than proportional to the increases in dose.

Conclusions: Results indicate that further clinical investigation of BAY 43-9006 is warranted, and suggest it could be a promising future therapy for patients with cancer.

Key words: BAY 43-9006, pharmacokinetics, phase I, safety

Introduction

Several molecular pathways play key roles in cancer, including signal transduction pathways, cell-cycle control pathways, apoptotic pathways, and the processes of angiogenesis and metastasis. Research in molecular biology has identified several important mediators of these pathways, which now represent potential targets for innovative anticancer treatments.

The G protein Ras is activated in response to receptor tyrosine kinase (RTK) stimulation, and activates downstream signaling cascades. One of the best characterized of these cascades is the Raf/MEK/ERK signaling pathway, which has a pivotal role in cell-cycle regulation and proliferation. Mutations in the ras gene are found in ~30% of all human cancers, and in a higher proportion of pancreatic and colon cancers, leading to uncontrolled proliferative signals [1]. In addition, the Raf/MEK/ERK pathway can be activated through mutations in Raf and overexpression of RTKs located in the plasma membrane, such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR-β) [2–5]. Raf has also been shown to contribute to protecting cells from apoptosis [6, 7]. Therefore, the Raf/MEK/ERK signaling cascade represents an important target for novel anticancer therapies [8, 9].

Angiogenesis is key to tumor growth and metastasis, and is mediated by the release of growth factors (VEGF, PDGF-β and basic fibroblast growth factor), which stimulate surrounding endothelial cells. These growth factors and their receptors also represent therapeutic targets.

BAY 43-9006 is an oral multi-kinase inhibitor that targets serine-threonine kinases and RTKs, and has effects on the tumor and vasculature. It prevented tumor growth in preclinical models by inhibition of tumor cell proliferation and neoangiogenesis. In preclinical studies, BAY 43-9006 induced potent inhibition of...
Raf kinase in vitro and in vivo, with dose-dependent antitumor activity in several human tumor types, including colon, pancreatic, lung and ovarian carcinomas [10]. BAY 43-9006 also demonstrated antitumor activity against established colon and ovarian tumors in xenograft models, which included some tumor regressions [10, 11]. It was well tolerated and there was no evidence of toxicity, as measured by drug-related lethality or increased weight loss relative to control animals. In these xenograft models, antitumor activity was observed in cancers that had activating Ras mutations, as well as in those cancers in which overexpression of growth factor receptors increased signaling through Raf [10–13].

BAY 43-9006 has been shown to produce anti-angiogenic effects in animal models, which could be mediated by inhibition of endothelial cell VEGFR-2 signaling [10, 14]. Since inhibition of Raf can also inhibit VEGF-mediated endothelial cell angiogenesis [15], BAY 43-9006 could be exerting its effects via VEGFR-2 and/or at the level of Raf.

BAY 43-9006 has been well tolerated in preclinical studies to date. In dogs, it was not associated with deleterious effects on pulmonary function, hemodynamics, cardiac contractility and electrocardiogram at doses up to 60 mg/kg (unpublished data). However, daily 10 mg/kg BAY 43-9006 doses were associated with enhanced alanine aminotransferase and lactate dehydrogenase in dogs (unpublished data). The starting dose of 50 mg every 4 days utilized in the present study is an extrapolation from the preclinical findings in dogs, based on the assumption that the oral bioavailability of BAY 43-9006 would be similar in humans. The chosen starting dose was predicted to have a therapeutic effect, while exhibiting low toxicity. Preliminary phase I studies with BAY 43-9006 100 mg twice daily showed that this dose was within the predicted therapeutic range and well tolerated, suggesting that the starting dose selected for the present study was conservative [16].

Results of preclinical studies suggest that BAY 43-9006 exerts a cytostatic effect, whereby tumor growth is reduced with treatment, but returns to baseline rates when the drug is withdrawn. Since a compromise must be achieved between minimizing the period off drug and avoiding potential toxicities associated with extended exposure, it is important to determine the maximum tolerated dose (MTD) and the optimal treatment regimen. Therefore, in this phase I study, which was part of a series of studies, dose escalations were performed to determine the safety, MTD, pharmacokinetics and efficacy of BAY 43-9006. In this study, BAY 43-9006 was administered orally to evaluate the optimum treatment regimen and dose for future phase II trials, in repeated cycles of 35 days (28 days on drug/7 days off) in patients with advanced, refractory cancer. The MTD, to be recommended for use in phase II studies, was considered to be the highest dose of BAY 43-9006 achieved without signs of unacceptable toxicity.

**Patients and methods**

**Patient selection**

Patients with documented evidence of incurable advanced, metastatic or recurrent solid tumors refractory to available therapy were enrolled. All patients were heavily pretreated, and met the following criteria: age ≥16 years; Eastern Cooperative Oncology Group performance status ≤2; life expectancy of at least 12 weeks; presence of clinically and/or radiologically assessable disease; and adequate bone marrow, liver and renal function. All patients gave written informed consent. Additional consent was obtained for biopsies and tumor samples. This study received institutional ethical approval, and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Individuals who fulfilled any of the following criteria were not eligible for admission to the study: pregnant or lactating women; patients receiving concurrent treatment or treatment within 30 days of screening with other experimental drugs or anticancer therapy; symptomatic or untreated brain metastases; serious illness or medical condition that would not permit the patient to be managed according to the protocol; immunotherapy or chemotherapy within 4 weeks of study entry; radiotherapy within 3 weeks of study entry; and previous exposure to Raf kinase inhibitors or similar compounds.

**Treatment plan**

This was an open-label, single-arm, dose-escalation study of BAY 43-9006 administered orally in repeated cycles of 35 days (28 days on/7 days off treatment), which was conducted at two Canadian sites (Princess Margaret Hospital, Toronto, and Juravinski Cancer Centre in Hamilton, Ontario), between December 2000 and January 2003. Three to four patients were initially enrolled in each group; treatment of each patient with BAY 43-9006 continued until unacceptable toxicity, tumor progression, patient withdrawal or death. Eight dose levels were utilized: 50 mg every 4 days, 50 mg every other day, 50 mg once daily, 100 mg once daily, 100 mg twice daily, 200 mg twice daily, 400 mg twice daily and 600 mg twice daily. A conservative starting dose of 50 mg every 4 days was chosen as it was predicted to be within the therapeutic range without being excessively toxic, based on preclinical studies in dogs and assuming that oral bioavailability of BAY 43-9006 is similar in humans compared with dogs. Subsequent groups were treated according to a standardized dose escalation scheme, depending on the worst toxicity experienced by individuals enrolled at the prior dose level, and the clinical significance of that toxicity (Figure 1). Toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0 [17].

In the absence of DLT within the first 28 days following commencement of treatment, dose escalation was employed, and the next group of three patients was enrolled at the next dose level. If DLT was seen in one of the three patients first enrolled in a given group, at least three further patients were enrolled at that dose level. If no DLT was experienced in the additional patients, dose escalation continued to the next dose level. If DLT occurred in at least two patients in the initial or extended group, dose escalation was stopped and that dose was designated as the MTD. If DLT was observed in at least two patients (within the first 28 days), or in the additionally enrolled patients (i.e. three or more patients in the extended group), the MTD for the schedule was considered to have been exceeded. Therefore, the previous dose level was declared as the MTD. Up to 10 additional patients could be enrolled at the identified MTD to obtain additional safety data. The MTD in this study was established as the recommended dose for use in further phase II studies. DLTs were adverse events considered to be related to the study drug, and defined as any of the following occurring during cycle 1: hematological toxicity (grade ≥3), non-hematological toxicity (grade ≥3), or clinically significant hematological or non-hematological toxicity considered by the primary investigator to warrant withholding the study medication and to be at least possibly related to study drug.

**Patient evaluation**

Baseline tumor measurements were obtained within 28 days before the start of treatment. Repeat tumor measurements were then obtained every 8 weeks...
for comparison. Tumor response and progression were evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) committee [18]. Changes in only the largest diameter (unidimensional measurement) of tumor lesions were used in RECIST. Baseline measurements of up to a maximum of 10 target lesions were recorded. These lesions were selected based on their size and suitability for accurate, repetitive measurements. The objective tumor response was measured using the baseline sum of longest diameters (LD) for all target lesions. Measurements were not made for non-target lesions, but these were noted at baseline and followed as either ‘present’ or ‘absent’.

The best response from each patient was classified according to the following criteria: complete response was defined as the disappearance of all clinical and radiological evidence of both target and non-target tumors; partial response was defined as ≥30% decrease in the sum of LD of target lesions; stable disease was defined as a tumor that had between a <30% decrease and <20% increase in the sum of LD; disease progression was defined as ≥20% increase in the sum of LD, taking as references the smallest sum LD recorded since initiation of treatment or appearance of any new lesions. Unequivocal progression of a non-measured lesion could be accepted as evidence of disease progression.

The duration of response was defined as the time period from the initial measurement of complete response/partial response (whichever was recorded first) to the first date that disease progression or recurrent disease was objectively documented. Duration of stable disease was measured from the start of therapy until the criteria for progression were met. The same method of assessment and the same techniques were used to characterize each identified and reported lesion at baseline and during follow-up.

Safety

Safety parameters were evaluated continuously throughout the study, and included results of physical examination, assessment of vital signs, and incidence of adverse events, DLTs and abnormal laboratory values.

Pharmacokinetics

Blood samples (5 ml aliquots) for the determination of plasma concentrations of BAY 43-9006 were collected on days 1 and 28 of each cycle. Samples were collected into a tube containing ammonium heparin, and centrifuged at 2800 g for 10 min at room temperature to separate the plasma. Samples were transferred to polypropylene tubes and frozen (−20°C or lower) until assayed.

The pharmacokinetic parameters measured were: area under the plasma concentration–time curve for 0–12 or 0–24 h (AUC0–12 or AUC0–24), maximum plasma concentration (Cmax), time to maximum concentration (tmax) and elimination half-life (t1/2). These parameters were correlated with systemic toxicities associated with the administration of BAY 43-9006, and appropriate pharmacodynamic parameters. BAY 43-9006 concentrations in plasma were determined using fully validated specific liquid chromatograph/tandem mass spectrometer methods, with a lower limit of quantitation of 0.001 µg/ml [19]. Based on quality-control samples that were assayed along with the samples, the intraday and interday precision for BAY 43-9006 analytes ranged from 1.0% to 15.1%, and the accuracy ranged from 86.7% to 114.7%.

Plasma concentration–time data were analyzed by non-compartmental methods using the WinNonlin 4.0 program. The linear-logarithmic trapezoidal method was used to calculate AUC, and t1/2 was calculated by linear regression of the terminal slope of the logarithmic plasma concentration–time profile.

Statistical analysis

A one-way analysis of variance was used to analyze the pharmacokinetic data. All continuous measurements were summarized by mean (or median for non-normal data), standard deviation, minimum and maximum. Categorical data were summarized by frequency counts and percentages. Pharmacokinetic, safety, laboratory and demographic data were all summarized by group.

Results

Patients’ characteristics

Out of 42 patients enrolled in this study, 41 received BAY 43-9006 and were evaluated for pharmacokinetic and safety analyses and one withdrew consent. Patients’ baseline characteristics are shown in Table 1. The most common primary tumor sites were colon (41%) and ovary (24%). The predominant metastatic sites of disease at study entry were liver, lung and pelvis.

It must be noted that all patients were heavily pretreated before enrolment in this study, and the number of prior anticancer systemic therapy regimens was not limited by the study.

Figure 1. Dose escalation schema.
protocol. A total of 39 patients (95%) had received surgery before enrolment in this trial; 38 patients (93%) had received prior chemotherapy; and 14 patients (34%) had been treated previously with radiotherapy.

Dose escalation

The numbers of treatment cycles received by patients are shown in Table 2. The maximum number of cycles received by any patient was 18 (50 mg once daily group), while 30 patients (73%) received three or fewer cycles of treatment. Nine patients (22%) received at least five cycles of treatment.

Dose escalations, reductions or interruptions were made in a total of 26 patients (63%); 20 patients (49%) had a dose reduction or interruption due to an adverse event. There were dose reductions in six patients (15%) due to toxicity [four patients experienced hand–foot skin reaction (HFS); one patient had changes in bilirubin; and one patient had constipation and abdominal pain].

DLTs, MTD and safety profile

Of the 42 patients enrolled in this study, 41 received at least one dose of study treatment and were evaluated for safety. One DLT (grade 3 fatigue) was observed at 200 mg twice daily, whereas no DLTs were experienced in the 400 mg twice daily group. Three DLTs (all HFS) were observed in the 600 mg twice daily group, necessitating discontinuation of the study drug. Therefore, the MTD, and the recommended dose for use in further studies, was established to be 400 mg twice daily.

All 41 patients (100%) experienced at least one treatment-emergent adverse event at any grade; 32 patients (78%) reported treatment-emergent adverse events at grade 3 or 4. Thirty-six patients (88%) reported at least one drug-related adverse event at any grade (Table 3). The most commonly reported drug-related adverse events at any grade included dermatological (dry skin, HFS, pruritus and rash), fatigue and gastrointestinal events (diarrhea, nausea and anorexia). There was an apparent increase in the frequency and severity of skin toxicity at doses at or exceeding 400 mg twice daily; however, there was no obvious dose-dependent change in the incidence of gastrointestinal toxicity. A total of 14 patients (34%) experienced drug-related adverse events at grade 3 or 4, and the most commonly reported were HFS and fatigue.

Ten patients (24%) discontinued study medication because of either a drug-related adverse event (six patients) or an adverse event that could be associated with disease progression (four patients). Eight deaths were observed, all of which occurred

### Table 1. Patients’ baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>37 (90)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>52.4 (33–70)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (54)</td>
</tr>
<tr>
<td>1</td>
<td>13 (32)</td>
</tr>
<tr>
<td>2</td>
<td>6 (15)</td>
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<tr>
<td>Previous therapy [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>39 (95)</td>
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<tr>
<td>Chemotherapy</td>
<td>38 (93)</td>
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<tr>
<td>Radiotherapy</td>
<td>14 (34)</td>
</tr>
<tr>
<td>Primary tumor type</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Ovary</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Kidney</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cervix</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Breast</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Uterus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown primary</td>
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</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status.

### Table 2. Number of cycles in each group

<table>
<thead>
<tr>
<th>Number of cycles</th>
<th>50 mg q4d (n = 3)</th>
<th>50 mg qod (n = 6)</th>
<th>50 mg qd (n = 4)</th>
<th>100 mg qd (n = 4)</th>
<th>100 mg bid (n = 3)</th>
<th>200 mg bid (n = 6)</th>
<th>400 mg bid (n = 8)</th>
<th>600 mg bid (n = 7)</th>
<th>Total (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>2</td>
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<td>≥5</td>
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<td>–</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Mean</td>
<td>3.7</td>
<td>2.0</td>
<td>7.3</td>
<td>6.3</td>
<td>3.0</td>
<td>2.0</td>
<td>3.8</td>
<td>2.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Median (min., max.)</td>
<td>2 (1, 8)</td>
<td>2 (1, 3)</td>
<td>4.5 (2, 18)</td>
<td>3.5 (1, 17)</td>
<td>3 (2, 4)</td>
<td>2 (1, 3)</td>
<td>3 (1, 9)</td>
<td>2 (1, 7)</td>
<td>2 (1, 18)</td>
</tr>
</tbody>
</table>

q4d, every 4 days; qod, every other day; qd, once daily; bid, twice daily.
after the end of treatment. None of these events was considered related to study drug. There was no apparent relationship between safety observations and pharmacokinetic findings.

Pharmacokinetics
Pharmacokinetic data were available for 34 patients. The plasma concentration–time profile of BAY 43-9006 was characterized by a relatively slow absorption phase, with occasional secondary peaks observed 6–12 h after dosing. An exponential decrease in plasma concentrations of BAY 43-9006 was generally observed 24–72 h after the last dose on day 28.

The pharmacokinetic parameters of BAY 43-9006 are presented in Table 4. There was considerable interpatient variability in the pharmacokinetics of BAY 43-9006. There was a substantial increase in BAY 43-9006 $C_{\text{max}}$ and AUC values over the dosing period (Table 4). BAY 43-9006 appeared to increase less than proportionally with increasing dose, however, and exhibited variation in its accumulation, with mean $t_{1/2}$ values ranging from 19.7 to 35.5 h. At the MTD of 400 mg twice daily, the mean $t_{1/2}$ was 27.4 h. The mean plasma AUC$_{0-12}$ and $C_{\text{max}}$ and median $t_{\text{max}}$ values for BAY 43-9006 400 mg twice daily on day 1 were 21.8 mg h/l, 2.9 mg/l and 2.9 hours, respectively. These mean values increased to 47.8 mg h/l, 5.4 mg/l and 12.1 h, respectively, on day 28. BAY 43-9006 accumulated in the plasma (i.e. AUC$_{0-12}$) 9.15-, 3.47-, 2.87- and 4.42-fold after multiple dosing with 100, 200, 400 and 600 mg twice daily, respectively. These AUC$_{0-12}$ values of BAY 43-9006 accounted for 90.1% of total exposure on day 1, and 78.9% of total exposure on day 28.

In order to determine the impact of interpatient variability, the relationship between BAY 43-9006 exposure and clinical safety was evaluated. Available data, although limited, do not suggest a relationship between drug-related adverse events, dose and the extent of BAY 43-9006 exposure. Therefore, the interpatient variability in BAY 43-9006 pharmacokinetics does not affect its clinical safety. There also appeared to be no relationship between baseline demographic variables (such as age, gender and body weight) and BAY 43-9006 exposure.

Response to therapy
The best response observed in this study was stable disease in nine patients (22%); disease progression occurred in the remaining
on 21 April 2018

qd, once daily; bid, twice daily; AUC 0–12 or AUC0–24, area under the plasma concentration–time curve for 0–12 or 0–24 h.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>AUC (mg/l)</th>
<th>Cmax (mg/l)</th>
<th>tmax (h)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n [geo. mean (approx. CV%)]</td>
<td>n [geo. mean (approx. CV%)]</td>
<td>n [median (range)]</td>
<td>n [geo. mean (approx. CV%)]</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Day 28</td>
<td>Day 1</td>
<td>Day 28</td>
<td>Day 1</td>
</tr>
<tr>
<td>50 qd</td>
<td>3 [8.44 (31.9)]</td>
<td>2 [5.46 (85.1)]</td>
<td>3 [0.58 (33.3)]</td>
<td>2 [0.34 (61.0)]</td>
</tr>
<tr>
<td>50 qod</td>
<td>3 [15.13 (27.0)]</td>
<td>4 [14.33 (53.6)]</td>
<td>6 [0.51 (94.9)]</td>
<td>4 [0.87 (58.4)]</td>
</tr>
<tr>
<td>50 qd</td>
<td>4 [6.49 (47.2)]</td>
<td>4 [15.29 (52.0)]</td>
<td>4 [0.43 (63.0)]</td>
<td>4 [1.03 (54.3)]</td>
</tr>
<tr>
<td>100 qd</td>
<td>3 [8.75 (35.1)]</td>
<td>4 [15.06 (64.6)]</td>
<td>4 [0.81 (37.6)]</td>
<td>4 [0.85 (62.0)]</td>
</tr>
<tr>
<td>100 bid</td>
<td>2 [6.13 (74.0)]</td>
<td>3 [45.98 (36.7)]</td>
<td>3 [0.81 (61.3)]</td>
<td>3 [5.48 (38.9)]</td>
</tr>
<tr>
<td>200 bid</td>
<td>4 [10.88 (38.4)]</td>
<td>5 [34.72 (43.8)]</td>
<td>6 [1.34 (33.8)]</td>
<td>5 [3.95 (52.3)]</td>
</tr>
<tr>
<td>400 bid</td>
<td>4 [21.81 (58.8)]</td>
<td>3 [47.78 (24.0)]</td>
<td>4 [2.87 (68.4)]</td>
<td>3 [5.37 (41.0)]</td>
</tr>
<tr>
<td>600 bid</td>
<td>3 [10.06 (96.7)]</td>
<td>5 [38.09 (36.8)]</td>
<td>7 [2.00 (71.5)]</td>
<td>5 [4.71 (28.5)]</td>
</tr>
</tbody>
</table>

AUC0–12 is reported for bid dosing; AUC0–24 is reported for all other dosing schedules.

AUC, area under the plasma concentration–time curve; Cmax, maximum plasma concentration; tmax, time to maximum concentration; t1/2, elimination half-life; approx. CV%, approximate coefficient of variation; geo. mean, geometric mean; q4d, every 4 days; qod, every other day;

The observed slow absorption and the substantial accumulation of BAY 43-9006 upon multiple dosing (AUC and Cmax) may have contributed to the incidence of manageable drug-related toxicities, such as diarrhea. Although there was interpatient variability in the AUC and Cmax of BAY 43-9006, this did not appear to result in clinically relevant toxicity.

Discussion

The results of this phase I study show that BAY 43-9006 at doses up to 400 mg twice daily is well tolerated in patients with advanced solid tumors when administered orally for 28 days consecutively followed by a 7-day rest period. BAY 43-9006 has a slow absorption phase and accumulates upon multiple dosing, although shows considerable interpatient variability in its pharmacokinetics. BAY 43-9006 also showed preliminary antitumor activity, by inducing disease stabilization.

The most common drug-related adverse events included skin toxicities, fatigue and gastrointestinal disorders. These were generally mild to moderate in severity and easily manageable. There was an apparent dose-related increase in the frequency and severity of skin-related adverse events, especially at the level of 400 mg twice daily and above. HFS and fatigue were the most frequently reported grade 3 and 4 drug-related adverse events. There were only six discontinuations due to drug-related events. Only four DLTs were reported during this study, three of which were at the 600 mg twice daily dose level. No DLTs were observed at 400 mg twice daily; therefore, this dose was established as the MTD. Since this MTD was consistent with the findings from three other phase I trials with different dosing schedules, the 400 mg twice daily dose was recommended for further evaluation in phase II/III trials [16].

32 patients (78%). Stable disease was achieved at all doses tested, with the exception of 50 mg every 4 days and 50 mg every other day. The median duration of stable disease was 7.2 months. Six patients (15%) stayed on study drug for more than 30 weeks; two received 50 mg once daily, and one each received 50 mg every other day, 100 mg once daily, 400 mg twice daily and 600 mg twice daily. Four of these six patients had ovarian cancer, and the other two had colon cancer and cancer of the peritoneum. The median time to disease progression for all 41 patients was 63 days.

Table 4. Plasma BAY 43-9006 pharmacokinetic parameters over the 28-day dosing period

The most common drug-related adverse events included skin toxicities, fatigue and gastrointestinal disorders. These were generally mild to moderate in severity and easily manageable. There was an apparent dose-related increase in the frequency and severity of skin-related adverse events, especially at the level of 400 mg twice daily and above. HFS and fatigue were the most frequently reported grade 3 and 4 drug-related adverse events. There were only six discontinuations due to drug-related adverse events. Only four DLTs were reported during this study, three of which were at the 600 mg twice daily dose level. No DLTs were observed at 400 mg twice daily; therefore, this dose was established as the MTD. Since this MTD was consistent with the findings from three other phase I trials with different dosing schedules, the 400 mg twice daily dose was recommended for further evaluation in phase II/III trials [16].

The observed slow absorption and the substantial accumulation of BAY 43-9006 upon multiple dosing (AUC and Cmax) may have contributed to the incidence of manageable drug-related toxicities, such as diarrhea. Although there was interpatient variability in the AUC and Cmax of BAY 43-9006, this did not appear to result in clinically relevant toxicity.

BAY 43-9006 showed preliminary evidence of antitumor activity, mainly by inducing clinically relevant stabilization of progressive disease, rather than tumor regression, suggesting that it has a primarily cytostatic effect. BAY 43-9006 showed activity against several different solid tumor types, with stable disease occurring as the best response in nine (22%) patients. Data from all four phase I studies evaluating different dosing regimens of BAY 43-9006 monotherapy revealed an overall mean stable disease rate of 40%, with 25% of patients maintaining a response for >6 months, and 6% for >12 months [16]. This suggests that BAY 43-9006 monotherapy results in a sustained cytostatic effect. In those studies, confirmed partial responses were experienced by one patient with renal cell carcinoma (RCC) in the 21 days on/7 days off dosing schedule, and one patient with hepatocellular carcinoma (HCC) on the continuous dosing schedule [16]. BAY 43-9006 is currently being evaluated in phase II/III trials for the treatment of RCC and HCC.

Neovascularization is essential for tumors to grow beyond 1–2 mm in diameter and to metastasize [20]. In addition to inhibiting Raf kinase, BAY 43-9006 also induces anti-angiogenic effects by inhibiting VEGFR and PDGFR-β tyrosine kinases. RCCs are highly vascularized solid tumors, in which mutations in the von Hippel–Lindau tumor suppressor gene (in clear-cell RCC) can result in overproduction of VEGF that is associated with a more aggressive tumor phenotype [21]. Increased activation of the Raf/MEK/ERK pathway has also been linked to elevated production of VEGF and increased angiogenesis [22–24].

In conclusion, BAY 43-9006 was well tolerated, with an antitumor effect in patients with advanced refractory solid tumors. The MTD of BAY 43-9006 was determined to be 400 mg twice daily.

Raf/MEK/ERK pathway has also been linked to elevated expression of VEGF that is associated with a more aggressive tumor phenotype [21]. Increased activation of the Raf/MEK/ERK pathway has also been linked to elevated production of VEGF and increased angiogenesis [22–24].

In conclusion, BAY 43-9006 was well tolerated, with an antitumor effect in patients with advanced refractory solid tumors. The MTD of BAY 43-9006 was determined to be 400 mg twice daily.
daily, and this dose is recommended for evaluation in phase II/III trials. These findings suggest that BAY 43-9006 has potential utility as a monotherapy in several solid tumor types, and that it warrants further clinical development.

References